MTF Formulary Management for Angiotensin Receptor Blocker / Calcium Channel Blocker Combinations (ARB/CCB Combos) and Renin Angiotensin Antihypertensives (RAAs)

Department of Defense Pharmacoeconomic Center

- **Azor and Exforge are not cost effective relative to using generic amlodipine with a formulary ARB or ACE inhibitor.**
- **Consider an ARB in patients intolerant of ACE inhibitors.**
- **For patients requiring an ARB for hypertension, maximize use of telmisartan (Micardis) and telmisartan / HCTZ.**
- **The direct renin inhibitor aliskiren +/- HCTZ (Tekturna) is not cost effective relative to the ARBs or ACE inhibitors.**

Uniform Formulary Decision: The Director, TMA approved recommendations from the June 2008 DoD P&T Committee meeting. The implementation period must be completed by 26 Nov 08.

Uniform Formulary (UF) Agents		Non-Formulary Agents
RAAs on BCF MTFs must have on formulary	**RAAs not on BCF MTFs may have on formulary**	**MTFs must not have on formulary**
ACE Inhibitors Captopril (generic) Lisinopril (generic) Lisinopril + HCTZ (generic) *ARBs* Telmisartan (Micardis) Telmisartan + HCTZ (Micardis HCT) *ACE/CCB combos* Benazepril+amlodipine (Lotrel generic)	*ACE Inhibitors* Captopril + HCTZ (generic) Benazepril; Benazepril + HCTZ (generic) Enalapril; Enalapril + HCTZ (generic) Fosinopril; Fosinopril + HCTZ (generic) Quinapril; Quinapril + HCTZ (generic) Trandolapril (Mavik) *ARBs* Candesartan (Atacand) Candesartan + HCTZ (Atacand HCT) Losartan (Cozaar) Losartan + HCTZ (Hyzaar) *Direct Renin Inhibitors* Aliskiren (Tekturna); UF Aug 07 Aliskiren + HCTZ (Tekturna HCT); UF Jun 08	*ARB/CCB Combos* Olmesartan + amlodipine (Azor); NF Jun 08 Valsartan + amlodipine (Exforge); NF Nov 07 *ACE Inhibitors* Moexipril (Univasc) Moexipril + HCTZ (Uniretic) Perindopril (Aceon) Ramipril (Altace) *ARBs* Eprosartan (Teveten); + HCTZ (Teveten HCT) Valsartan (Diovan); + HCTZ (Diovan HCT) Olmesartan (Benicar); + HCTZ (Benicar HCT) Irbesartan (Avapro); + HCTZ (Avalide) *ACE/CCB combos* Trandolapril/verapamil (Tarka) Enalapril/felodipine (Lexxel) – discontinued

Renin Angiotensin Antihypertensive Agents (RAAs)

- The Renin Angiotensin Antihypertensive Agents (RAAs) class includes the ACE inhibitors, ACE / HCTZ combinations, ACE / calcium channel blocker (CCB) combinations, angiotensin (ARBs), ARB / HCTZ combinations, ARB / CCB combinations, direct renin inhibitors (DRIs), and DRI / HCTZ combinations. The RAAs class was designated at the May 2007 DoD P&T Committee meeting in anticipation that new products (e.g., ARB/CCB combinations, DRI/CCB combinations) would be entering the market.

ARB / CCB Combinations *(reviewed Nov 2007 and June 2008)*

- Olmesartan/amlodipine (Azor) and valsartan/amlodipine (Exforge) were designated as non-formulary at the Jun 08 and Nov 07 meetings, respectively. Azor and Exforge are solely approved for treating hypertension. Clinical trial data comparing Exforge to lisinopril +HCTZ found similar (but not greater) reductions in blood pressure (BP). Clinical trials evaluating Azor to antihypertensive agents other than the individual components have not been published.
- Administering a formulary ARB with generic amlodipine will produce the same reduction in BP as giving Azor or Exforge, at a significantly reduced cost to the MTFs. If a CCB combination product is required, benazepril/amlodipine (generic Lotrel) is available on the BCF.
- Current Joint National Commission (JNC VII) guidelines for treating hypertension recommend that most patients receive therapy with a regimen containing a thiazide diuretic. There are several UF ACE + HCTZ and ARB + HCTZ fixed dose combinations to choose from.

ACE Inhibitors *(date of original DoD P&T review: Aug 2005)*

- Generic formulations of ramipril (Altace) are now commercially available. The P&T Committee will re-examine ramipril's formulary status when the price of the generic becomes cost effective and supply issues are resolved.
- Quinapril (Accupril) and quinapril/HCTZ (Accuretic) were changed from non-formulary to formulary status at the Feb 08 meeting, due to market entry of cost effective generic formulations.

- The ACE inhibitors continue to remain the most cost effective RAA (lisinopril average weighted cost $0.05/day) for treating all disease states (hypertension, chronic heart failure, diabetic renal disease). ARBs should be reserved for patients intolerant of ACE inhibitors. About 5-10% of patients discontinue an ACE inhibitor due to cough.

ARBs *(date of original DoD P&T review: Feb 2005; date of re-review: May 2007)*

- Hypertension trials show that one ARB reduces blood pressure just as well as another when compared at equivalent doses. All ARBs have similar safety and tolerability profiles. Telmisartan /+ HCTZ (Micardis, Micardis HCT) is the most cost-effective ARB for HTN at $0.21/day.
- Telmisartan now has outcomes data showing that it reduces the risk of cardiovascular death in high risk patients. The ONTARGET trial (NEJM 10 Apr 2008) evaluating telmisartan with ramipril or a combination of telmisartan plus ramipril was similar to the landmark HOPE ramipril trial in terms of patient population (e.g., at high cardiovascular [CV] risk, and primary endpoint (composite of death from CV causes, MI, stroke, or hospitalization for HF). Telmisartan was non-inferior to ramipril in preventing the primary endpoint. The combination of ACE plus ARB showed no difference in preventing the primary endpoint.
- For heart failure patients intolerant of ACE inhibitors, consider candesartan ($0.56/day). There are no data to suggest clinically significant differences between candesartan (Atacand) and valsartan (Diovan) in treating chronic HF, based on the results of the CHARM and Val-HEFT trials.
- For type 2 diabetic nephropathy patients, consider losartan ($0.50/day). There are no data to suggest clinically significant differences between losartan (Cozaar) and irbesartan (Avapro) in treating type 2 diabetic nephropathy, based on the results of the RENAAL and IDNT trials.
- Valsartan is approved for use in patients following an MI; however, more evidence exists for the use of ACE inhibitors in this population. The Medical Necessity process can be used to obtain valsartan for post-MI patients.

ACE/CCB Combos *(date of original DoD P&T Committee review: Feb 2006)*

- The BCF product amlodipine/benazepril (Lotrel) was reported to produce a greater reduction in cardiovascular outcomes (death, fatal/non-fatal MI and stroke) in patients older than 60 years than benazepril/HCTZ in a report at the March 2008 American College of Cardiology meeting; the study (ACCOMPLISH) has not yet been published. The study was terminated early due to the benefit of Lotrel. Until the results are available in a peer-reviewed publication, no change from JNC VII guidelines are recommended.
- The NF product enalapril/felodipine (Lexxel) has been discontinued voluntarily by the manufacturer.

Direct Renin Inhibitors (DRIs) *(Reviewed at Aug 2007 and Jun 2008 DoD P&T Committee)*

- Aliskiren (Tekturna) and aliskiren /HCTZ (Tekturna HCT) are the first direct renin inhibitors to receive FDA approval. Both products are solely indicated for treating hypertension.
- Tekturna has been compared to ARBs (losartan, irbesartan, valsartan), ramipril and HCTZ in clinical trials. A similar (but not greater) degree of BP reduction was seen with Tekturna vs. it comparators. Tekturna HCT results in a greater reduction in BP than administering the individual components as monotherapy.
- The product labeling for both Tekturna and Tekturna HCT lists the same precautions regarding teratogenicity, hyperkalemia, and elevations in serum creatinine as the ACE inhibitors and ARBs.
- Studies assessing the benefits of aliskiren on cardiovascular outcomes such as death, stroke, or myocardial infarction are underway. However, only studies assessing surrogate endpoints (e.g., regression of left ventricular hypertrophy, reduction in urinary albumin to creatinine ration, reduction of B-type natriuretic peptide in HF) have been published.
- Tekturna and Tekturna HCT are less cost effective than the other RAAs included on the UF. The most appropriate place in therapy for the DRIs in treating hypertension remains to be determined.

Medical Necessity

- Medical necessity criteria apply to Azor, Exforge, Teveten, Teveten HCT, Diovan, Diovan HCT, Benicar, Benicar HCT, Avapro, Avalide, Univasc, Uniretic, Aceon, Altace and Tarka. Specific criteria are available on the TRICARE Pharmacy website at www.tricare.mil/pharmacy/medical-nonformulary.cfm.

Renin Angiotensin Antihypertensive Agents (RAAs) Price Comparison at MTF	
Drug	**Weighted Avg. Cost/Day (April 2008)[a/b]**
Basic Core Formulary RAAs	**MTF Cost**
Captopril	$0.04
Lisinopril + HCTZ	$0.05
Telmisartan + HCTZ (Micardis, Micardis HCT)	$0.21
Benazepril + amlodipine	$0.46
Uniform Formulary RAAs	
Captopril + HCTZ	$0.28
Benazepril + HCTZ	$0.18
Enalapril + HCTZ	$0.07
Fosinopril +HCTZ	$0.43
Quinapril + HCTZ	$0.76
Trandolapril (Mavik)	$0.50
Candesartan + HCTZ (Atacand, Atacand HCT)	$0.56
Losartan + HCTZ (Cozaar, Hyzaar)	$0.50
Aliskiren + HCTZ (Tekturna, Tekturna HCT)	$0.66
Non-Formulary RAAs	
Olmesartan + amlodipine (Azor)	$1.79
Valsartan + amlodipine (Exforge)	$1.88
Moexipril + HCTZ (Univasc, Uniretic)	$0.37
Perindopril (Aceon)	$0.42
Ramipril (Altace)	$0.74
Eprosartan + HCTZ (Teveten; Teveten HCT)	$0.88
Irbesartan + HCTZ (Avapro, Avalide)	$0.97
Olmesartan + HCTZ (Benicar, Benicar HCT)	$0.77
Valsartan + HCTZ (Diovan, Diovan HCT)	$1.35
Trandolapril + verapamil (Tarka)	$1.19

[a] Post-decision prices; actual price may vary slightly due to MTF-specific Prime Vendor discounts and/or fees
[b] MTFs are prohibited from entering into any incentive pricing agreements in any form with ARB pharmaceutical manufacturers to receive additional discounts.
[C] System costs are the average weighted daily cost across all 3 points of service (MTF, Retail Network, TMOP)

References

- DoD P&T Committee minutes are available at http://www.pec.ha.osd.mil/PT_Committee.htm
- Current/future drug classes under review by the DoD P&T Committee: www.pec.ha.osd.mil/PTCommittee.htm
- TRICARE website for information on the Uniform Formulary: www.tricare.osd.mil/pharmacy
- TRICARE Formulary Search Tool: www.tricareformularysearch.org

For more information about this drug class review, email the PEC Staff at: PECUF@amedd.army.mil.